Psalmacross: A Novel Tarantula Venom-Derived Peptide Drug Candidate for ASIC Inhibition via in silico Design

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Acid-sensing ion channels (ASICs) are proton-gated, voltage-insensitive transmembrane proteins activated in acidic conditions, playing crucial roles in neuronal signaling. ASIC subunit 1a is highly expressed in the amygdala, a brain region responsible for fear regulation. Thus, ASIC1a is a promising therapeutic target for anxiety and depression disorders. Psalmotoxin, a peptide in Psalmopoeus cambridgei tarantula venom, is a potent, specific ASIC1a antagonist. However, its clinical efficacy is limited by poor blood-brain barrier (BBB) permeability. This study engineered a novel psalmotoxin derivative, Psalmacross, through computational simulations, addressing the BBB limitation while preserving ASIC1a inhibition. Alanine scanning was conducted through AlphaFold and ChimeraX, identifying residues essential for ASIC1a binding while substituting non-critical residues with alanine, lowering predicted toxicity. To aid BBB penetration, the peptide Angiopep-2 was attached to the N-terminus of psalmotoxin, enabling transcytosis through low-density lipoprotein receptor-related protein 1. ToxinPred toxicity prediction scores indicated Psalmacross to likely be non-toxic. Protein-protein docking through HADDOCK and PRODIGY showed that Psalmacross maintained strong binding to ASIC1a. Molecular dynamics simulations performed with CHARMM-GUI, OpenMM, and VMD confirmed the structural stability of the Psalmacross-ASIC1a complex under conditions similar to the human brain's physiology. Thus, Psalmacross has the potential to be a stable, low-toxicity, BBB-permeable ASIC1a inhibitor, representing a promising template for future therapeutics. Additionally, as Psalmacross is a peptide, it could be sustainably and easily produced through genetic engineering, augmenting its impact.

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